Knoll Pharmaceutical Company

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September 24, 1999

Docket Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Supplement to Citizen Petition 96P-0243
Bioequivalence Requirements for Propafenone Tablets

Dear Sir/Madam:

Knoll Pharmaceutical Company submits herewith, in duplicate, a supplement to the subject petition originally submitted on June 28, 1996.

Sincerely,

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA:dsb

enc.

96P-0243 Supl

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A SUPPLEMENT TO
PROPAFENONE CITIZEN'S PETITION

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I. INTRODUCTION

Knoll Pharmaceutical Company ("Knoll") submits herewith this supplement to its Citizen Petition (96P-0243 submitted on June 28, 1996; hereinafter called "The Petition") concerning bioequivalence requirements for propafenone tablets. Knoll holds an NDA (#19,151) for Rythmol® (propafenone hydrochloride) tablets, and believes that one or more Abbreviated New Drug Applications may be pending which specify Rythmol as the reference listed drug.

In this supplement, Knoll provides additional reasons why FDA should require that bioequivalence studies of propafenone meet the stated criteria. Knoll also now specifically requests that the FDA not approve new or pending ANDA for a propafenone tablet unless the bioequivalence studies submitted in the ANDA satisfy the criteria proposed in the Petition and this supplement.

In the Petition, Knoll requested FDA that an amendment to the bioequivalence requirements be promulgated for propafenone HCl as per the FDA regulations [21 CFR 320.32(c)]. This supplement is to present the FDA with subsequent bioavailability/bioequivalence guidances issued by the FDA and others that reinforced the need for specific bioequivalence tests, given the unique pharmacokinetic properties of propafenone.

Knoll requests that the FDA shall consider the factors cited in this supplement according to 21 CFR320.33 in evaluating the criteria and evidence to assess actual or potential bioequivalence problems for propafenone tablets.

Propafenone is a class 1C antiarrhythmic drug approved for the treatment of **life threatening documented ventricular arrhythmia**. The therapeutic effect of propafenone (safety and efficacy) was shown to be related to its plasma concentrations (page 12 of the Petition). Therefore, **lack of bioequivalence would have serious adverse effects in the treatment**. This is one of the factors to be considered in the criteria and evidence to assess actual or potential bioequivalence problems [12 CFR 320.33(d)]. The other factors under 21 CFR 320.33 that apply to propafenone are:

- 21 CFR 320.33(f)(3) "There is rapid metabolism of the therapeutic moiety in the intestinal wall or liver during the process of absorption (**first-pass effect**) so the therapeutic effect and/or toxicity of such drug is determined by the rate as well as the degree of absorption."

- 21 CFR 320.33f(6) "The drug product is subject to **dose-dependent kinetics** in or near the therapeutic range, and the rate and extent of absorption are important to bioequivalence."

Propafenone is a drug with a complicated pharmacokinetic profile (i.e. non-linear pharmacokinetics, active metabolites contributing to safety and efficacy, and high

variability in metabolism). In the Petition, we have provided the scientific background for propafenone pharmacokinetic complexities and requested you to consider four elements prior to approval of generic propafenone formulations. Since our previous submission, we note that several regulatory guidance documents[1-6] have been issued by the FDA and Canadian Drugs Directorate to address bioavailability/bioequivalence issues related to complex pharmacokinetics of drugs such as propafenone.

This supplement to the Petition cites regulatory guidances and data in support of an amendment to the bioequivalence requirements to require the following five elements[a] prior to approval of Propafenone products.

1. **Single-dose bioequivalence study of the approved Rythmol® tablet and the proposed generic formulation at the low and high dose if dosage forms are composition proportional or at each dosage strength if dosage forms are not composition proportional.**

2. **Steady state bioequivalence studies of sufficient size to include a representative number of subjects classified as "slow" or "poor" metabolizers at the low and high dose; or at each dosage strength if dosage forms are not composition proportional;**

3. **Bioequivalence to the reference listed drug (Rythmol®) should be evaluated with respect to both the parent compound, propafenone and its two active metabolites, 5-hydroxypropafenone (5-OHP) and N-depropylpropafenone (NDPP).**

4. **Bioequivalence to the reference drug (Rythmol®) should be evaluated after single dose and at steady state at least at the highest dose with respect to the effects of food on the plasma levels of propafenone and its active metabolites. Data developed by Knoll indicate that propafenone bioavailability does not change in a food/fasting study during chronic administration but food has a pronounced effect on bioavailability in single dose studies.**

5. **Substitution of multiple units for a higher dose should not be allowed until dosage form equivalency is established between 2 X 150 mg tablets and 1 x 300 mg Rythmol® or generic 300 mg propafenone tablet.**

These recommendations are based on regulatory guidances available in the US and Canada to address the following pharmacokinetic characteristics of propafenone.

[a] Knoll is not suggesting that these elements necessitate separate studies. Properly designed studies could incorporate multiple elements.

- Extensive first pass metabolism.
- High inter-subject variability due to metabolic polymorphism.
- Dose-dependent kinetics in the suggested dosing range (i.e. a drug with non-linear kinetics).
- Two active metabolites that significantly contribute to safety and efficacy; for one of the metabolites (5-OHP), the metabolite to parent concentration ratio changes over the suggested dosing range.
- Significant food effect on pharmacokinetics of propafenone following a single dose but not after multiple dosing.
- The efficacy and safety of propafenone are related to plasma concentrations of propafenone and its metabolites.

A majority of the data related to the scientific aspects of propafenone was submitted in the Petition.

All the regulatory references cited in this supplement are attached in the Appendix.

In Knoll's view, these are the minimum requirements to establish bioequivalence of propafenone formulations if they are to be therapeutically interchangeable. The basis for these proposed requirements is discussed below.

II. STATEMENT OF GROUNDS

A. Need for Special Requirements for a Single-Dose Bioequivalence Study

This study is a basic requirement suggested by the Agency to compare pharmaceutical equivalents[5]. In the Petition (dated June 28, 1996), we have suggested the basic design for this study (i.e. two-period, two-treatment, two-sequence, randomized, crossover design).

However, based on the draft bioequivalence guidance for industry issued recently[5], the preferred study design is a single-dose, two-treatment, four-sequence, four-period, randomized, crossover study under fasting conditions, comparing equal doses of the test substance and a reference product. This four-period design was specifically suggested by the FDA in a guidance document issued for industry for oral immediate release products of phenytoin[1], a drug with nonlinear kinetics similar to propafenone

Generally, when the dosage forms are ingredient proportional among dosage forms, a single dose bioequivalence study at the highest dose is conducted according to CFR 320.22 (d)(2). However, this concept only works well for drugs with linear pharmacokinetics.

Due to nonlinearity in the pharmacokinetics of propafenone (PPF) which is metabolized to an active metabolite, 5-hydroxy propafenone (5-OHP), the variability in Cmax and AUC of the PPF and 5-OHP and the ratios of 5-OHP/PPF at the high dose (300 mg) could be different from those at low dose. Therefore, test products and Rythmol® should be compared at low (150 mg) and high (300 mg) strengths. Unless the active to inactive ingredients are proportional for the generic test products, a waiver for bioequivalence requirements cannot be granted for the intermediate strength, 225 mg (i.e. bioequivalence needs to be established between a test product and Rythmol® at 225 mg strength) according to CFR 320.22 (d)(2). In addition, the Canadian bioequivalence requirements for drugs exhibiting nonlinear pharmacokinetics[3] also require bioequivalence to be studied at each dosage strength if the dosage forms are not compositionally proportional. Thus, if generic formulations are not compositionally proportional among 150, 225, and 300 mg dosage forms, it is imperative that bioequivalence should be established between test products and Rythmol® at each dosage strength, especially considering the active metabolite, high metabolic variability and nonlinear kinetics of propafenone.

B. Need for Bioequivalence Studies at Steady State: Studies Should Include a Representative Number of Subjects Classified as Slow Metabolizers

The need for a steady-state bioequivalence study was previously documented in the Petition. It was shown that the metabolite to parent plasma concentration ratios depend on the propafenone concentration. The metabolite half-lives were longer than propafenone. Considering the nonlinearity of propafenone due to saturation of the metabolic pathway to 5-hydroxypropafenone, it would be very difficult to predict the extent of differences in rate or extent of absorption at steady-state from single dose studies. Similarly, it would be difficult to predict steady-state concentrations of parent and metabolites from one dose level to the other because of nonlinearity and heterogeneity in metabolism. Therefore, it is necessary to compare the steady-state concentrations following multiple dosing of test and reference products at low and high doses if compositionally proportional, and at every dosage strength if not compositionally proportional in representative populations (slow and fast metabolizers) to assess the impact of metabolic differences. The

Canadian Expert Advisory Committee on bioavailability for drugs that exhibit nonlinearity (Report C)[4] suggests the following:

- *The bioavailability of at least the lowest and highest dosage strengths should be studied.*

- *For those drugs, which demonstrate non-linear kinetics at any clinically relevant dose, chronic dose studies may be required.*

Therefore, a multiple dose study showing bioequivalence between test and reference products, in terms of parent and metabolite concentrations in slow and fast metabolizers, is essential. Results of this study would also be useful for the determination of switchability of propafenone products by physicians or pharmacists.

C. Need for Bioequivalence Studies to Measure Active Metabolites of Propafenone

In the Petition, we have presented data (Griani et. al.)[7] to show that 5-OHP amounts to 24% of PPF at Cmax at steady-state (300 mg tid X 1 month) and amounts to 43% of PPF following a single 300 mg dose. We have also provided data to show that relative potencies of 5-OHP and NDDP were 80% and 25%, respectively, compared to propafenone. Together, these observations provide evidence that metabolites contribute significantly to the therapeutic effect of propafenone. A recent FDA draft guidance document[5] states:

"*If the degradant and/or metabolite contributes meaningfully to safety and/or efficacy, the degradant and/or metabolite should be measured to ensure bioequivalence*".

In addition, the FDA's comments on a bioequivalence study protocol[2] clearly states that both metabolites of propafenone (5-OHP and NDDP) should be monitored.

Consequently, parent and metabolites should be measured in bioequivalence studies.

D. Need for Multiple-Dose Studies to Evaluate Effects of Food on Bioavailability

Food effect BE studies are needed by the FDA unless the drug products have all the characteristics described in Section II (E) of the FDA draft guidance on food-effect BA/BE studies[6]. The Canadian Expert Advisory Committee (Report C)[4], addressing nonlinear drugs, also suggested to conduct bioequivalence studies under fasting and fed conditions. The FDA

in their review of a BE study protocol for propafenone 300 mg tablets[2] requested the firm to conduct a single-dose three-way crossover food effect BE study (test formulation under fast, test formulation with food, and reference formulation with food).

However, in the Petition, we have shown data to indicate that food increases the bioavailability of propafenone only after a single dose but not after multiple dosing. As food effects are generally a result of changes in absorption, hepatic blood flow, and saturable metabolism, it would be hard to predict the extent of food effect for each propafenone formulation at steady-state based on single dose data. In addition, it would be hard to predict food effects from the lower dose to a higher dose. Therefore, food effect BE studies at least at the highest dose following single and multiple dosing are necessary to establish bioequivalence of new propafenone formulations to a reference product under fed conditions.

E. Dosage Form Equivalency

Propafenone is currently marketed in the U.S. as 150, 225 and 300 mg tablets. There is a high likelihood that manufacturers may choose to have one or more formulations to go to market. If only one strength is to be approved, it is advisable to allow the use of that tablet only for that dose level. For example, substitution of two 150mg tablets for a 300-mg unit should not be allowed unless they are shown to be bioequivalent. If a single strength is to be approved, appropriate labeling should be in place to warn not to substitute multiple units for a single higher strength.

III. SUMMARY

In summary, all propafenone pharmacokinetic/pharmacodynamic data, relevant to bioequivalence issues, were submitted to the FDA in the Petition. The Petition contained data concerning the use of propafenone in ventricular arrhythmia, a serious condition, and also contained data on systemic drug exposure variability from patient to patient in terms of propafenone and its active metabolites. In this Supplement, we have looked for regulatory guidances related to drugs with similar characteristics as propafenone. Knoll therefore requests that the Agency, in conformity with 21 CFR 320.32 and 21 CFR 320.33, promulgate an Amendment to the bioequivalence requirement for propafenone to require the following elements for approval of an ANDA for propafenone:

1. **Single-dose bioequivalence study of the approved Rythmol® tablet and the proposed generic formulation at the low and high dose if dosage forms are composition proportional; or at each dosage strength if dosage forms are not composition proportional.**

2. **Steady state bioequivalence studies of sufficient size to include a representative number of subjects classified as "slow" or "poor" metabolizers at the low and high dose; or at each dosage strength if dosage forms are not composition proportional;**

3. **Bioequivalence to the reference listed drug (Rythmol®) should be evaluated with respect to both the parent compound, propafenone and its two active metabolites, 5-hydroxypropafenone (5-OHP) and N-depropylpropafenone (NDPP).**

   The proposed studies would show that the drug product for which an ANDA is being requested is bioequivalent to the reference listed drug (Rythmol®) and its metabolites during single dosing and at steady state. The rate and extent of absorption must be compared with the reference product under fasting conditions. Mean steady-state plasma concentrations of propafenone, 5-OHP and NDPP should be compared between products.

4. **Bioequivalence to the reference drug (Rythmol®) should be evaluated after single dose and at steady state at least at the highest dose with respect to the effects of food on the plasma levels of propafenone and its active metabolites. Data developed by Knoll indicated that propafenone bioavailability does not change in a food/fasting study during chronic administration, but food has a pronounced effect on bioavailability in single dose studies.**

   The proposed study should show that the drug product for which an ANDA is being submitted is bioequivalent to the reference listed drug by producing equivalent blood concentrations of propafenone and its two active metabolites to the innovator's Rythmol®.

5. **Substitution of multiple units for a higher dose should not be allowed until dosage form equivalency is established between 2 X 150 mg tablets and 1 x 300 mg Rythmol® or generic 300 mg propafenone tablet.**

   This is to ensure that prescribers and pharmacists will not substitute two 150 mg generic propafenone tablets for a single 300-mg Rythmol® tablet without proper *in vivo* studies showing bioequivalence.

IV. REFERENCES

1. Interim guidance, phenytoin/phenytoin sodium capsules, tablets and suspension, In vivo bioequivalence and in vitro dissolution testing; Office of Generic Drugs, CDER, FDA (March 4, 1994).

2. Protocol review package, Propafenone hydrochloride tablets, 300 mg, Office of Generic Drugs, CDER, FDA (January 31, 1996).

3. Bioequivalence requirements: Drugs exhibiting non-linear pharmacokinetics, Drugs Directorate, Ontario, Canada (January 13, 1997).

4. Report C, Expert advisory committee on bioavailability, Health protection branch, CANADA (December 1992).

5. Draft guidance for Industry on BA and BE studies for orally administered drug product, General Considerations; Federal Register, September 2, 1999 (Volume 64, Number 171, page 48409-48410).

6. Draft Guidance for Industry, Food-Effect bioavailability and bioequivalence studies, CDER, FDA (October 1997).

7. Giani P, Landolina M, Giudici V, et al. Pharmacokinetics and pharmacodynamics of propafenone during acute and chronic administration. Eur J clin Pharmacol 1998; 34:187-194.